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DESCRIPTION

NOVEL CRYSTAL

Technical Field

5 The present invention relates to a novel crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide useful as an inhibitor of Ca^{2+} release-activated Ca^{2+} channel.

10 Background of the Invention

 It is known that Ca^{2+} release-activated Ca^{2+} channel (abbreviated as CRACC hereinafter; also called store-dependent Ca^{2+} channel) exists in almost all inflammatory cells such as mast cells, lymphocytes and astrocytes (J. Biol. Chem., 270, p29-32 (1995)). It is also reported that 15 it is deeply involved in cytokine production, lipid mediator release, and the like (J. Immunol., 155, p286-96 (1995) and Br. J. Pharmacol., 144, p598-601 (1995)).

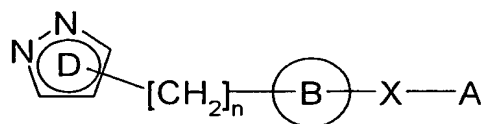
 Additionally, it is known that CRACC exists also in 20 endothelial cells (Am. J. Physiol., 269, C733-8 (1995)) and epithelial cells (J. Biol. Chem., 270, p169-75 (1995)). It has been reported that sustained calcium influx is involved in the radical damage of endothelial cells (Am. J. Physiol., 261, C889-896 (1991)), suggesting that CRACC 25 inhibitors have protective efficacy on endothelial cell-concerned tissue damages. Further, it has been reported

that blockages of calcium influx inhibit cell proliferation and interleukin-2 (IL-2) production (Br. J. Pharmacol., 133, p861-8 (1994)). CRACC inhibitors are useful as agents for preventing and treating proliferative or progressive
5 diseases such as malignant tumors and autoimmune diseases and are also useful as suppressors for tissue rejection on transplantation.

Therefore, it is expected that CRACC inhibitors can be pharmaceutical agents useful for preventing or treating
10 various inflammatory diseases, allergic diseases, autoimmune diseases, tissue damages, proliferative diseases, and the like.

A pyrazole derivative having a high inhibition selectivity for CRACC over voltage-operated Ca^{2+} channel
15 (abbreviated as VOCC hereinafter) involved in intracellular calcium regulation of excitatory cells such as smooth muscle cells and nerve cells and having an inhibitory activity against IL-2 production has been reported (for example, patent reference 1).

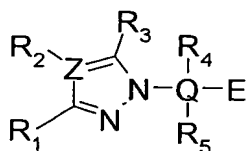
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(In the formula, D represents pyrazolyl which may be substituted with halogeno-lower alkyl, or the like; n represents 0 or 1; B represents for example phenylene; X
25 represents for example $-\text{NR}^1-\text{CR}^2\text{R}^3-$; A represents for example

monocyclic or bicyclic or tricyclic fused heteroaryl which may have one or more substituents; see the official gazette about the detail.)

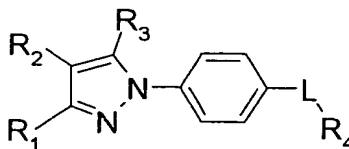
Additionally, other pyrazole derivatives having an inhibitory activity against IL-2 production and being useful as an agent for treating autoimmune diseases have also been reported (for example, patent references 2 and 3). The patent reference 2 discloses the following compound.



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(In the formula, R₁ and R₃ represent for example perfluoroalkyl with 1 to 15 carbon atoms; Z represents nitrogen or carbon; Q represents for example aryl; and E represents for example -L₃-B; see the official gazette about the detail.)

The patent reference 3 discloses the following compound.



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(In the formula, R₁ and R₃ represent for example CF₃; and L represents for example -NHC(O)-; see the official gazette about the detail.)

4,6-Dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide may be included in the claims of patent references 1 to 3, but it is a novel compound which is not specifically disclosed therein.

5 Patent reference 1

Pamphlet of International Publication No. 99/19303

Patent reference 2

Pamphlet of International Publication No. 99/51580

Patent reference 3

10 Pamphlet of International Publication No. 99/62885

When a compound is to be used as a pharmaceutical product, generally, the compound is used preferably in the form of crystal from the standpoint of stability. For handling and constant quality, additionally, it is
15 sometimes necessary to control the crystal polymorphism of the compound.

Disclosure of the Invention

The present inventors made studies for the purpose
20 of providing a novel pharmaceutical product selectively inhibiting CRACC and being useful for preventing and treating various inflammatory diseases and allergic diseases. As a result, the inventors obtained 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide as a crystal and found unexpectedly that
25 the crystal of the compound includes two polymorphic types.

Further, the inventors found that any of the polymorphic crystals was preferable as a raw material for producing pharmaceutical compositions.

Specifically, the invention relates to the
5 polymorphic crystals of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide useful as a raw material for producing pharmaceutical compositions.

The invention will be explained below in detail.

10 The invention relates to the crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide. The crystal of the invention may be stable enough to be used as a raw material for producing pharmaceutical products and is particularly preferably α
15 type or β type crystal having the following physicochemical values. Each of the crystals is characterized by the following X-ray powder diffraction patterns [$2\theta(^{\circ})$].

Herein, interplanar spacings and overall pattern are important for identification of crystal in the X-ray powder
20 diffraction, due to the characteristic of the data.

Because relative intensity changes more or less, depending on the crystal growth direction, particle size and measuring conditions, the relative intensity should not be understood strictly.

25 α type: 5.94, 9.94, 15.64, 15.88, 18.48, 20.04 and 20.76.

β type: 10.60, 12.90 and 17.24.

By the DSC analysis, the α type crystal has an endothermic peak at about 196°C (onset: the temperature at which peak rises). The β type crystal has a very small peak around 172 to 174°C based on phase transition and further has an endothermic peak at about 196 °C (onset). In other words, both the α type and β type crystals have endothermic peaks at 195°C to 198°C (onset).

Because both the α type and β type crystals are stable at 5 to 60°C for at least three months and can be highly purified by recrystallization, these crystals may be used as raw materials for producing pharmaceutical products. Particularly, these crystals are preferable as raw materials for producing solid pharmaceutical preparations.

The results of a stability test, for example, at 40°C under light-resistant are shown in Table 1.

Table 1

Stability test at 40°C under light-resistant

	After 1 month	After 3 months
α type crystal	100.7%	99.2%
β type crystal	99.7%	100.7%

(The values express the assay values determined by an internal standard method on the basis of peak area obtained by HPLC)

The α type crystal can be obtained by recrystallization in toluene. Additionally, the α type crystal may also be obtained by stirring a suspension of
5 the β type crystal in a mixed solvent of 2-propanol and water at room temperature to under heating, preferably at 30 to 60°C, more preferably at 40 to 50°C for several hours to several days. In other words, the α type crystal is a crystal form which is suitable for large-scale production
10 in view of the stability in a suspension.

The β type crystal can be obtained by adding water (preferably, water of an equal volume to that of 2-propanol) to the 2-propanol solution with stirring. In
15 other words, the β type crystal is excellent in that the crystal can be produced directly using a solvent with lower toxicity than that of toluene and the like.

For recrystallization of any of the α type and β type crystals, it is preferable to use the intended crystal separately obtained as a seed crystal.

20 By dissolving such crystal under heating, using a mixed solvent of 2-propanol and water (for example, at a mixing ratio of 4:3, respectively), and cooling the resulting solution with standing to allow the crystal to precipitate, a crystal having the same thermal absorption
25 peak as the α type crystal in the DSC analysis and the same diffraction pattern as that of the α type crystal except

for the peak at $2\theta = 19.24^\circ$ in the X-ray powder diffraction may sometimes be obtained. The crystal is stable at room temperature. Based on the results of the DSC analysis and X-ray powder diffraction thereof, the crystal is also
5 included in the α type crystal of the present invention.

Additionally, the present invention relates to a solid pharmaceutical composition comprising the crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide and a pharmaceutically acceptable
10 carrier.

Industrial Applicability

4,6-Dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide is excellent in terms of the
15 CRACC inhibitory activity, the inhibition selectivity over VOCC, and the activity of suppressing IL-2 production. Further, it exerted very good activities at tests described in the patent reference 1, including an effect on the suppression of TNFB-induced Contact Hypersensitivity, an
20 activity of suppressing the arthritis in murine collagen-induced arthritis model, an activity of suppressing of antigen-induced airway eosinophilia (rat) and the like. Therefore, a pharmaceutical product containing the compound is useful as an agent for preventing or treating allergic,
25 inflammatory or autoimmune diseases in which CRACC and IL-2 participates. Herein, the allergic, inflammatory or

autoimmune diseases include, for example, bronchial asthma, psoriasis, atopic diseases including atopic dermatitis, inflammatory bowel diseases including Crohn disease, digestive ulcer, nephritis, hepatitis, pancreatitis, collagenosis, rheumatoid arthritis, osteoarthritis, and rejection on transplantation. The usefulness on these diseases can be confirmed at the *in vitro* tests of the CRACC inhibitory activity and the activity of suppressing IL-2 production as described in the patent reference 1 and at various tests using, for example, antigen-induced airway eosinophilia model as a typical disease model of bronchial asthma, and murine collagen-induced arthritis model. 4,6-Dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide may be produced by the method described in the patent reference 1.

The solid pharmaceutical composition comprising the crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide as the active ingredient of the present invention may be prepared by methods for general use, using pharmaceutical carriers, excipients and the like for general use in the field. Dosing may be carried out by any dosage forms for oral administration in the forms of tablets, pills, capsules, granules, powders, liquids, and the like, or parenteral administration in the forms of injections into joints, veins, muscles, and the like, suppositories, transdermal liquids, ointments, transdermal

attachments, transmucosal liquids, transmucosal plasters, inhalation agents, and the like. Particularly, tablets, pills, capsules, granules, powders, and the like for oral administration and inhalation agents, transnasal agents, and the like for parenteral administration using the crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide as a raw material for the production thereof are advantageous as stable solid formulations.

For a solid formulation for oral administration, the compound of the present invention is mixed with at least one inert excipient, such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone and magnesium aluminate metasilicate. The composition may contain inert additives, for example, lubricants such as magnesium stearate, disintegrators such as sodium carboxymethyl starch, and auxiliary dissolution agents according to general methods. If necessary, the tablets or pills may be coated with sugar coating or coated with coating agents soluble in stomach or intestine.

The liquid composition for oral administration includes, for example, pharmaceutically acceptable emulsions, liquids, suspensions, syrups and elixirs and contains inert solvents for general use, for example distilled water and ethanol. The composition may contain

auxiliary agents such as solubilizers, moistening agents and suspending agents, sweeteners, flavors, aromatic agents and preservatives.

The injections for parenteral administration include
5 sterile, aqueous or non-aqueous liquids, suspensions, and emulsions. The aqueous solvent includes, for example, distilled water for injections and physiological saline. The non-aqueous solvent includes, for example, propylene glycol, polyethylene glycol and vegetable oils such as
10 olive oil, alcohols such as ethanol, and polysorbate 80 (product name). Such composition may additionally contain isotonic agents, preservatives, moistening agents, emulsifying agents, dispersants, stabilizers and auxiliary dissolution agents. These are sterilized by filtration
15 through bacteria-trapping filters, blending of sterilizing agents or irradiation. Additionally, these may be used by firstly making into aseptic solid compositions and then dissolving or suspending them in sterile water or sterile solvents for injection use prior to their use.

20 Transmucosal agents such as inhalation agents and transnasal agents in solid, liquid or semi-solid forms are used and can be produced by the known methods. For example, excipients such as lactose and starch and pH adjusters, preservatives, surfactants, lubricants,
25 stabilizers and thickeners may appropriately be added. For the administration, appropriate devices for inhalation or

insufflation may be used. For example, using known devices, such as inhalation device for measured administration, and sprayers, the compound may be administered singly or may be administered in a powder form of a formulated mixture or in solution or suspension in combination with pharmaceutically acceptable carriers. The inhalation devices for dry powder and the like may be devices for single administration or plural administrations. Dry powder or powder-containing capsule may be used. Otherwise, the compound may be administered in the form of appropriate sprays, such as aerosol spray under pressure, using appropriate gases such as chlorofluoroalkane, hydrofluoroalkane or carbon dioxide.

The dose is appropriately determined, depending on each case in terms of the symptom, age, sex, etc. of a subject to be administered. For the oral administration, generally, the dose is about 0.001 mg/kg to 10 mg/kg per adult per day, which is administered in one portion or two to four portions. For inhalation, the dose is within a range of 0.0001 mg/kg to 1 mg/kg per adult per administration, which is administered once or several times a day.

Brief Description of the Drawings

Fig. 1

X-ray powder diffraction chart of the α type crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide.

Fig. 2

5 Thermal analysis chart of the α type crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide.

Fig. 3

10 X-ray powder diffraction chart of the β type crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide.

Fig. 4

15 Thermal analysis chart of the β type crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide.

Best Mode for Carrying out the Invention

20 The invention is now described specifically in the following Examples, which never limit the scope of the invention.

Measurement of the X-ray powder diffraction was carried out, using a sample which had been ground according to the conventional method and MXP18TAHF22 manufactured by MAC Science under the following conditions: anode: copper; 25 tube current: 350 mA; tube voltage: 45 kV; sampling

interval: 0.020°; scanning speed: 3.0°/min; wavelength:
1.54056 angstroms; scanning range (2θ): 5 to 40°.

Differential scanning calorimetry (DSC) and
thermogravimetry (TG) were performed, using DSC2910 and Hi-
5 Res TGA 2950 manufactured by TA Instruments under the
following conditions: sample amount: about 5 mg; sample
container: aluminium pan (open; for DSC) and platinum pan
(open; for TG); heating rate: 10°C/min; temperature range
for measurement: room temperature to 250°C; atmospheric
10 gas: dried nitrogen; and flow rate of atmospheric gas: 50
ml/min.

Example 1

Oxalyl chloride (8.7 ml) was added to a mixture of
15 4,6-dimethylnicotinic acid (15.1 g) and dichloromethane
(150 ml) under ice cooling, followed by stirring at 15 to
20°C for one hour. A mixture of 4-[3,5-
bis(trifluoromethyl)-1H-pyrazol-1-yl]aniline (23.59 g) and
dichloromethane (300 ml) was added to the resulting
20 reaction solution, followed by stirring at room temperature
for 18 hours. An aqueous 20% potassium carbonate solution
(about 200 ml) was added to the reaction solution, from
which the organic layer was separated. Subsequently, the
aqueous layer was extracted with dichloromethane (about 50
25 ml). The organic layer and the extract solution were
combined together and subsequently concentrated under

reduced pressure. The resulting residue was recrystallized from a mixed solvent (270 ml) of ethanol and water (2:1, respectively), to obtain 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide (26.70 g) as bluish white solid.

FAB-MS(Pos.) : m/z 429[(M+H)⁺] ; NMR(DMSO-d₆) δ : 2.41 (3H, s), 2.49(3H, s), 7.24(1H, s), 7.60(2h, d, J=8.8Hz), 7.79 (1H, s), 7.95 (2H, d, J=8.8Hz), 8.58 (1H, s), 10.72 (1H, s).

Example 2

(Production of the α type crystal)

A mixture of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide (8.0 g) and toluene (160 ml) was heated until the solution boiled. Subsequently, the resulting solution was stirred overnight with a spinbar, while allowing the solution to cool to room temperature. The precipitated crystal was collected by filtration, washed with toluene (10 ml) and dried overnight at 60°C under reduced pressure, to obtain the α type crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide (6.52 g) as white solid.

Example 3

(Production of the β type crystal)

2-Propanol (120 ml) was added to 4,6-dimethyl-4'-
[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide
(8.0 g), followed by dissolution and heating until the
solution boiled. Subsequently, the resulting solution was
5 left to stand for cooling to room temperature. No crystal
precipitation was observed. Under stirring with an
stirring wing, water (120 ml) was added to the solution and
the mixture was stirred at room temperature for one hour
and 30 minutes. The precipitated crystals were collected
10 by filtration, washed with a mixed solvent (about 50 ml) of
2-propanol and water (1:1, respectively), and dried at 60
°C under reduced pressure for one day, to obtain the β type
crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-
pyrazol-1-yl]nicotinilide (7.32 g) as white solid.

15

The crystals of 4,6-dimethyl-4'-[3,5-
bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide of the
present invention, particularly the α type and β type
crystals, are highly stable and useful as a raw material
20 for producing pharmaceutical products.